ATTACHMENT #4

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 850 Third Ave Brooklyn, NY 11232 718/340-7000	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Timothy Getek, Ph.D.	PERIOD OF INSPECTION 10/5...23/98	C. F. NUMBER 24-36921
TITLE OF INDIVIDUAL Associate Director Bioanalytical Lab.	TYPE ESTABLISHMENT INSPECTED Bioanalytical Lab	
FIRM NAME Forest/Inwood Laboratories, Inc.	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same	
STREET ADDRESS 220 Sea Lane	STREET ADDRESS OF PREMISES INSPECTED Same	
CITY AND STATE *(Zip Code)* Farmingdale, NY 11735	CITY AND STATE *(Zip Code)* Same	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Observations were made regarding studies [redacted] R/5000/0001, FLU-PK-03-000 (Rimantadine), and R/1700/004 (Isosorbide Dinitrate).

1. The SOP #F-001 entitled "Analytical Run Acceptance Criteria" is not objective in that it permits calibration standards to be deleted so that quality control (QC) values will fall within the acceptable limits. Examples include:

   a) [redacted] Stock Solution Stability: Run [redacted]

   b) [redacted] Runs [redacted]

2. SOP #F-001 permits calculation of accuracy of QCs using the validated QC value as the true value, rather than using the theoretical value. Calculation of accuracy using the theoretical value as the true value would result in the majority of QCs not meeting the acceptance criteria in about 50% of the analytical runs for [redacted] and [redacted]

3. The reported assay precision in the analytical runs was not accurate because the precision analysis did not include the standards and QCs which failed to meet the acceptance criteria. For example, inclusion of all standard values in [redacted] increased the coefficient of variation (CV) for [redacted] (from 2.5-10.2% to 2.5-**15.5%**) and for [redacted] (from 2.5-9.8% to 2.5-**12.0%**). Similarly, inclusion of all standard values in [redacted] increased the CV for [redacted] (from 3.6 - 9.6% to 3.6 - **18.3%**) and [redacted] (from 2.2 - 8.0% to 2.2 - **21.9%**).

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4. There was no established criteria for determining assay interference. About 30% of pre-dose samples in Study [redacted] had significant interference (> 33% of LOQ response) at the retention time of [redacted]

5. The acceptance criterion for validation on new QCs is not specific in that SOP #F-006 (section 4:01) fails to identify the number of new QCs that should be acceptable. In the mini-validation run dated 12/28/94 for ISDN, two of six low QCs were greater than the acceptance criteria. Further, there was an 11% difference between the new and old QCs in this run.

6. Reference standards used by the firm for analysis are accepted and used as 100% pure, although certificates of analysis, in certain instances, do not contain adequate data on the purity or potency of the standard. Examples include:

   a) Certificates of analysis for m-hydroxyrimantadine hydrochloride, lot FL-95-31, and p-hyroxyrimantadine hydrochloride, lot JS-111-99, used in study R/5000/0001, each reported that the thin-layer chromatographic test produced only one spot. There is no data to show that these tests will separate and determine the impurities of these reference standards. No other purity or potency test data were provided.

   b) The certificate of analysis for [redacted] batch 155/103, used in study [redacted] did not provide purity or potency data other than a thin-layer chromatographic test with results listed as "satisfactory".

7. Reference standards are used for analysis with an assumed 100% potency regardless of the actual potency/purity. In some instances there were significant

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discrepancies. Examples include;

a) For reference standard, [redacted] lot IW-MC-18, used in study ANC-[redacted] an HPLC purity determination indicated only 93.2% purity. The firm used the standard as 100% pure without including a purity correction factor in the calculations.

b) For reference standard, [redacted] lot P-2876, used in study [redacted], the certificate of analysis indicates 95% purity. The firm used this standard as 100% pure without including any purity correction factor.

8. Reference standards used for analysis are not dried prior to weighing nor are loss on drying or water factors used to correct the weights.

9. The firm's SOPs that address reference standards (#D-001) do not provide clearly defined acceptance criteria for non-USP standards.

10. Firm's SOPs allow for non-USP analytical reference standards, which are not covered by a supplier's assigned expiration date, to be used for up to [redacted] without re-testing or other available supporting stability data.

11. Reference standards are weighed on an analytical balance and the weights recorded to 4 decimal places (eg. 0.0100 g). Typically 10 milligrams of standard are weighed-out, however in some instances smaller quantities are weighed. Although management indicated that to avoid unacceptable error, a micro-balance would be used to weigh quantities less than 10 milligrams, instances were noted where smaller amounts of standards were weighed-out on the analytical balance. These include the weighing of 8.8 milligrams of para-

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hydroxyrimantadine hydrochloride standard on 5/3/96 and the weighing of 1.1 milligrams of [redacted] on 8/22/95.

12. Firm's SOPs allow for the stability of stock solutions to be checked by chromatographic comparison with the mix solution. This procedure is inadequate to assess stability, since both the stock and mix solutions are stored together under identical conditions.

13. Per SOP #D-001, the firm assigns a blanke[redacted] expiration date for all stock solutions and a [redacted] expiration date for all working and spiking solutions without supporting stability data.

14. Instances were noted where drug solutions were utilized beyond the expiry period allowed for in SOP #D-001 without required re-testing to assure stability of the analytes in solution. Examples include:

a) [redacted] stock solution , prepared on 8/22/95 by weighing 1.1mg into 5ml of methanol, was used in a total of [redacted] studies conducted between 10/95 and 12/97. In [redacted] of these studies the stock was used beyond the firm's [redacted] expiration date, and in [redacted] of these studies the stock was used 24 months or longer from the date of preparation. The firm does not have data to show that this solution is stable for this period of time.

b) [redacted] stock solution, prepared on 3/4/96, was used in [redacted], conducted from 6/11/97-7/23/97. This is past the firm's [redacted] expiration date for stock solutions and there is no data to show that the solution is stable for this period of time.

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c) Para-hydroxyrimantadine hydrochloride stock solution, prepared 5/3/96, was used in Rimantadine study FLU-PK-03-000, conducted 9/18/97-2/17/98. This is beyond the firm's [redacted] expiration date for stock solutions and there is no data to show that the solution is stable for this period of time.

15. The stock solutions for [redacted] made on 8/22/95, and for [redacted] made on 3/4/96, were each used for the preparation of both QC and standard curve solutions. The firm's SOPs require that separate stock solutions be used for the preparation of QC and standard curve solutions.

16. The firm's acceptance criteria for the injection of the mix solution at the beginning of the analytical run is not adequate to assure reproducibility of the chromatographic system.

17. For para-hydroxyrimantadine hydrochloride used in study FLU-PK-03-000, the calculated percentages of axial and equatorial isomers were 47.4 and 52.6 respectively. However, rather than using these actual calculated percentages, the firm used a [redacted] ratio in the study calculations.

18. Freezer and refrigeration units used to store study specimens and test solutions are not monitored by any continuous time/temperature recording devices. An alarm system is used to monitor these storage units 24 hours a day, however review of the alarm system records for 1997/1998 showed numerous instances where the alarms were activated. In most cases these alarm events were not adequately documented in that the extent and duration of the temperature failures, the cause of the problem, and the corrective actions taken (if any) were not recorded.

19. Firm's SOPs require calibration of the manually operated digital micro-pipettes

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only [redacted] This service has been provided by the pipette manufacturer, at the manufacturer's facilities. Calibration records show many instances where upon receipt by the manufacturer, initial examination of the pipettes found them out-of-specification for precision and/or accuracy. Since only [redacted] calibrations are performed, there is no way to determine when the units in question may have been in use for analytical purposes while out-of-specification. Additionally, when used in analytical procedures, firm's laboratory records do not identify the specific pipettes that were employed.

20. The following was noted regarding the multiprobe robotic micro-pipettor, and the automated solid phase extractors:

a) There are no written SOPs for the calibration of either the multiprobe robotic micro-pippettor, or the automated solid phase extractor units.

b) Firm's SOPs call for conducting [redacted] validation both on the multiprobe pipettor and on the automated solid phase extractors. Prior to this inspection, the most recent validation of the multiprobe pipettor was in May 1996. To date, no validation has been performed on any of the [redacted] solid phase extractors currently in-use at the firm.

c) The written SOPs and test data for the validation of the multiprobe pipettor do not specify any acceptance criteria for the test results obtained.

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